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Regulatory Issues: FDA

Benefit-Risk Summary of Regorafenib for the Treatment of Patients with Advanced Hepatocellular Carcinoma That Has Progressed on Sorafenib

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Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Hepatocellular carcinoma • Regorafenib • Sorafenib

Abstract

On April 27, 2017, the U.S. Food and Drug Administration approved regorafenib for the treatment of patients with advanced hepatocellular carcinoma (HCC) who had previously been treated with sorafenib. Approval was based on the results of a single, randomized, placebo-controlled trial (RESORCE) that demonstrated an improvement in overall survival (OS). Patients were randomly allocated to receive regorafenib160 mg orally once daily or matching placebo for the first 21 days of each 28-day cycle. The trial demonstrated a significant improvement in OS (hazard ratio [HR] = 0.63; 95% confidence interval [CI], 0.50–0.79, $p < .0001$) with an estimated median OS of 10.6 months in the regorafenib arm and 7.8 months in the placebo arm. A statistically significant improvement in progression-free survival (PFS) based on modified RECIST for HCC [Semin Liver Dis 2010;30:52–60] (HR = 0.46; 95% CI, 0.37–0.56, $p < .0001$) was also demonstrated; the estimated median PFS was 3.1 and 1.5 months in the regorafenib and placebo arms, respectively. The overall response rate, based on modified RECIST for HCC, was 11% in the regorafenib arm and 4% in the placebo arm. The toxicity profile was consistent with that observed in other indications; the most clinically significant adverse reactions were palmar-plantar erythrodysesthesia, diarrhea, and hypertension. Based on the improvement in survival and acceptable toxicity, a favorable benefit-to-risk evaluation led to approval for treatment of patients with advanced HCC. ***The Oncologist*** 2018;23:496–500

Implications for Practice: Regorafenib is the first drug approved by the U.S. Food and Drug Administration for the treatment of hepatocellular carcinoma that has progressed on sorafenib and is expected to become a standard of care for these patients.

Introduction

An estimated 39,230 new diagnoses of and 27,170 deaths due to liver and intrahepatic bile duct cancers occurred in the U.S. in 2016 [1]. The majority of these new cases and deaths are due to hepatocellular carcinoma (HCC), the most common primary cancer of the liver worldwide [2]. Overall for HCC in the U.S., the 5-year survival rate is approximately 12% [3]. Additionally, the incidence of liver cancer has been increasing in both men and women in the U.S. [1], and liver cancer is one of the most common causes of cancer deaths worldwide and led to approximately 700,000 deaths in 2008 alone [4]. Eastern and Southeastern Asia, Middle and Western Africa, Melanesia, and Micronesia and Polynesia have the highest incidence of liver cancer [4].

For patients with advanced or metastatic HCC and Child-Pugh class A cirrhosis, first-line systemic treatment consists of sorafenib, an oral multikinase inhibitor, at 400 mg twice daily, based on results of the SHARP study [5]. In that study, 602 patients with advanced HCC were randomized to receive sorafenib 400 mg twice daily or placebo. The SHARP trial demonstrated a significant improvement in overall survival (OS; hazard ratio [HR] 0.69; 95% confidence interval [CI], 0.55–0.87, $p < .001$). In addition to the SHARP study, the effects of sorafenib for the treatment of patients with advanced HCC were assessed in 226 patients in a randomized, placebo-controlled clinical trial conducted in China, South Korea, and Taiwan. In this trial, survival was also improved (HR 0.68; 95% CI, 0.50–0.93, $p = .014$) [6]. Based on the placebo arm of published reports of trials examining second-line agents for the treatment of HCC, the estimated median overall survival for patients with HCC that has progressed on sorafenib is approximately 7 to 9 months [7–9].

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This article was published online on 31 January 2018. An error was subsequently identified in Figure 1. This notice is included in the online and print versions to indicate that both have been corrected 7 February 2018.

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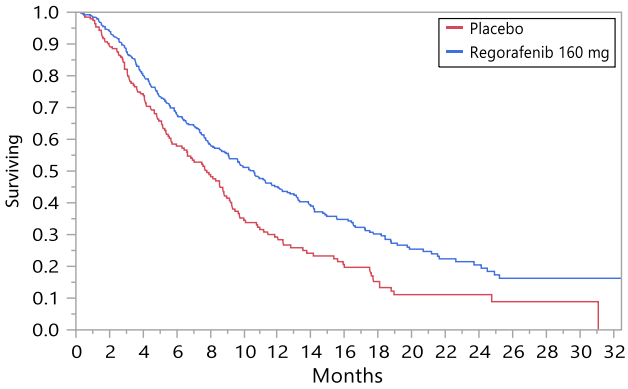
Table 1. Patient characteristics

Characteristics	Placebo ($n = 194$), *n* (%)	Regorafenib ($n = 379$), *n* (%)
Gender		
Male	171 (88)	333 (88)
Female	23 (12)	46 (12)
Age		
Range, years	23–83	19–85
Median, years	62	64
Younger than 65 years	116 (60)	199 (53)
Race		
Asian	78 (40)	156 (41)
Black or African American	2 (1)	6 (2)
White	68 (35)	138 (36)
Multiple	1 (0.5)	2 (0.5)
Not reported[a]	45 (23)	77 (20)
Region[b]		
Asia	73 (38)	143 (38)
Rest of the world	121 (62)	236 (62)
ECOG performance status[b]		
0	129 (66)	251 (66)
1	65 (34)	128 (34)
Etiology of HCC		
Hepatitis B	73 (38)	143 (38)
Hepatitis C	41 (21)	78 (21)
Alcohol use	55 (28)	90 (24)
AFP group[b]		
≥400 ng/mL	85 (44)	158 (42)
<400 ng/mL	106 (55)	216 (57)
BCLC stage at study entry		
A (early)	0 (0)	1 (0.3)
B (intermediate)	22 (11)	53 (14)
C (advanced)	172 (89)	325 (86)
Child-Pugh score at study entry		
A5	118 (61)	244 (64)
A6	70 (36)	129 (34)
B7	5 (3)	5 (1)
B8	1 (0.5)	0 (0)
Macrovascular invasion[b]		
Present	54 (28)	110 (29)
Absent	140 (72)	269 (71)
Extrahepatic disease[b]		
Present	147 (76)	265 (70)
Absent	47 (24)	114 (30)

[a]Not reported for all patients, in accordance with laws governing study sites in particular countries.
[b]Stratification factor.
Abbreviations: AFP, alpha fetoprotein; BCLC, Barcelona Clinic Liver Cancer; HCC, hepatocellular carcinoma.



Efficacy results	Placebo ($n = 194$), *n* (%)	Regorafenib ($n = 379$), *n* (%)
Alive	54 (28)	146 (39)
Dead	140 (72)	233 (61)
Median time to event (95% CI)	7.8 (6.3, 8.8)	10.6 (9.1, 12.1)
HR (95% CI)	0.63 (0.50, 0.79)	
p value (stratified log-rank test)	<.0001	

Figure 1. Efficacy results: primary endpoint, overall survival.
Abbreviations: CI, confidence interval; HR, hazard ratio.

Regorafenib (Stivarga; Bayer, Berlin, Germany) is an oral biaryl urea small molecule that targets multiple receptor tyrosine kinases, including members of the vascular endothelial growth factor receptor (VEGF) and platelet-derived growth factor receptor families [10]. Regorafenib was approved in the U.S. on September 27, 2012, for the treatment of patients with metastatic colorectal cancer who have been previously treated with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF therapy, and, if the disease is *KRAS* wild type, an anti-epidermal growth factor receptor therapy. On May 29, 2013, regorafenib was approved for the treatment of patients with locally advanced, unresectable or metastatic gastrointestinal stromal tumor who have previously been treated with imatinib mesylate and sunitinib malate.

In December 2012, the applicant submitted a new protocol to the U.S. Food and Drug Administration (FDA) for the study of regorafenib for the treatment of HCC. Orphan Drug Designation was granted for this indication in June 2015, and Priority Review was granted in December 2016. One study was submitted in support of the approval of regorafenib for the second-line treatment of patients with HCC. The results of this trial have been published [11]. This article summarizes the FDA's review of the data submitted in the supplemental New Drug Application and the basis for approval of regorafenib for this new indication.

The RESORCE Trial

Trial Design

RESORCE (REgorafenib after SORafenib in patients with hepatoCEllular carcinoma) was an international, randomized, double-blind, placebo-controlled trial comparing regorafenib with placebo in patients with HCC that had progressed on sorafenib therapy. A total of 573 patients were randomly allocated 2:1 to receive regorafenib 160 mg orally daily or placebo 160 mg orally daily on days 1 through 21 of each 28-day cycle until disease progression (radiologically or clinically) or unacceptable toxicity. Randomization was stratified based on geographical region (Asia vs. other regions), Eastern Cooperative Oncology Group (ECOG) performance status (0 vs. 1), alpha fetoprotein level (<400 ng/mL vs. ≥400 ng/mL), extrahepatic disease (presence vs. absence), and macrovascular invasion (presence vs. absence).

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Table 2. Efficacy results: secondary endpoints

Efficacy results	Placebo ($n = 194$), *n*		Regorafenib ($n = 379$), *n*
PFS by mRECIST			
PFS events, *n* (%)	181 (93)		293 (77)
Progressive disease	173		274
Deaths	8		19
mPFS, months (95% CI)	1.5 (1.4–1.6)		3.1 (2.8–4.2)
HR (95% CI)		0.46 (0.37–0.56)	
p value		<.0001	
PFS by RECIST			
PFS events	184 (95)		288 (76)
Progressive disease	175		270
Deaths	9		18
mPFS, months (95% CI)	1.5 (1.4–1.5)		3.4 (2.9–4.2)
HR (95% CI)		0.43 (0.35–0.52)	
p value[a]			
ORR by mRECIST			
Response rate, % (95% CI)	4.1 (1.8–8.0)		10.6 (7.6–14.1)
Responders (CR+PR)	8		40
CR	0		2
PR	8		38
p value[a]			
Median duration of response, months (95% CI)	2.7 (1.9–NE)		3.5 (1.9–4.5)
ORR by RECIST			
Response rate, % (95% CI)	2.6 (0.8–5.9)		6.6 (4.3–9.6)
Responders (CR+PR)	8		25
CR	0		0
PR	8		25
p value[a]			
Median duration of response, months (95% CI)	5.6 (2.3–NE)		5.9 (1.4–8.4)

[a]Because of the absence of alpha allocation for these tests, *p* values are not reported.
Abbreviations: CI, confidence interval; CR, complete response; HR, hazard ratio; mRECIST, modified RECIST; mPFS, median PFS; NE, not estimable; ORR, overall response rate; PFS, progression-free survival; PR, partial response.

Eligible patients must have been able to tolerate treatment with sorafenib (defined as not less than 20 days on at least 400 mg daily within the last 28 days prior to stopping the sorafenib) and must have had progressive disease on sorafenib. Other key inclusion criteria were Barcelona Clinic Liver Cancer category B or C, Child-Pugh class A cirrhosis, and ECOG performance status 0–1. Key exclusion criteria were prior systemic treatment for HCC except with sorafenib, permanent discontinuation of sorafenib therapy because of a sorafenib-related toxicity, esophageal varices at risk for bleeding that were not being treated with standard medical treatment, ascites not controlled with diuretic or paracenteses, active hepatitis B infection, and hepatitis C infection that required antiviral treatment.

The primary endpoint was OS, and key secondary endpoints included progression-free survival (PFS) and overall response rate (ORR) by investigator assessment using modified RECIST (mRECIST) for HCC criteria and RECIST version 1.1 criteria. Tumor assessments were performed every 6 weeks for the first eight cycles, then every 12 weeks thereafter. The assumptions for the study sample size of 560 patients were a true hazard ratio of 0.70 for overall survival, median survival of 8 months in the placebo arm and 11.4 months in the regorafenib arm, and a requirement for 370 deaths to provide 90% power to detect statistically significant difference in survival at a two-sided significance level of 0.05.

Results

A total of 573 patients were enrolled; 379 patients were randomized to the regorafenib arm and 194 patients to the placebo arm. Baseline demographic and disease characteristics, summarized in Table 1, were generally similar between the two arms and reflected those expected for the population of patients with HCC; however, the percentage of males was 88% in the RESORCE trial, whereas the male-female ratio in the HCC population was reported to be between 2:1 and 4:1 [12].

Efficacy

Efficacy results are summarized in Figure 1 (primary endpoint) and Table 2 (secondary endpoints). The RESORCE trial demonstrated statistically significant improvements in OS, PFS, and ORR. Using mRECIST for HCC and RECIST version 1.1 resulted in a similar estimation of PFS (HR = 0.46 [95% CI, 0.37–0.56] using

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Table 3. Grade 3–4 adverse events by preferred term (incidence ≥3%)

Preferred term	Grade 3–4, % of regorafenib ($n = 374$)	Grade 3–4, % of placebo ($n = 193$)
Hypophosphatemia[a]	34	7
Increased aspartate aminotransferase[a]	18	20
Increased blood bilirubin[a]	16	16
Hypertension	15	5
Increased lipase[a]	14	9
Palmar-plantar erythrodysesthesia syndrome	12	1
Asthenia and fatigue	10	5
Increased alanine aminotransferase[a]	7	5
Decreased platelet count[a]	6	0
Ascites	4	6
Anemia	4	6
General physical health deterioration	4	5
Hyponatremia	4	3
Diarrhea	3	0
Increased gamma-glutamyltransferase	3	3
Abdominal pain	3	3
Decreased appetite	3	2

[a]Values are based on laboratory test abnormality data as opposed to adverse event data.

mRECIST and HR = 0.43 [95% CI, 0.35–0.52] using RECIST version 1.1), whereas using RECIST version 1.1 resulted in a more conservative estimate of ORR (10.6% vs. 4.1% using mRECIST and 6.6% vs. 2.6% using RECIST version 1.1, for the regorafenib and placebo arms, respectively).

Safety

The primary safety population included 374 patients in the regorafenib group and 193 patients in the placebo group who received at least one dose of study drug in the RESORCE trial. The percentage of patients who experienced a serious adverse event were comparable between the two treatment groups. The most common adverse reactions of regorafenib (all grades) with a higher incidence compared with the placebo group were pain (55% vs. 44%), palmar-plantar erythrodysesthesia (PPES; 51% vs. 7%), asthenia/fatigue (42% vs. 33%), diarrhea (41% vs. 15%), hypertension (31% vs. 6%), infection (31% vs. 18%; fatal in 1.3% vs. 0%), and decreased appetite/food intake (31% vs. 15%). Cases of pancreatitis were also reported in 1.6% of patients in the regorafenib arm, and the U.S. Prescribing Information was updated to reflect this risk. Table 3 provides a summary of severe (grade 3–4) adverse events. Differences between the FDA's analysis and the data in the published report [11] occurred based on FDA grouping of certain terms (e.g., fatigue and asthenia) or the FDA's use of laboratory data to describe the laboratory findings.

Among regorafenib-treated patients, 48% had dose reductions because of an adverse event. The most common adverse reactions requiring dose modification (interruption or dose reduction) were PPES (21%), hyperbilirubinemia (6%), fatigue (5%) and diarrhea (5%). Treatment discontinuation occurred in approximately 10% of regorafenib-treated patients; the most common adverse reactions requiring discontinuation of regorafenib were PPES (2%) and increased aspartate aminotransferase (AST; 2%).

Discussion

For patients with HCC, the 5-year survival rate in the U.S. is approximately 12%. For patients with advanced HCC, the survival time is measured in months. Standard first-line therapy for advanced HCC is sorafenib, which extends patients' survival by approximately 2 to 3 months [5, 6]. The median survival for patients with HCC that progressed on sorafenib is approximately 8 months. Prior to the FDA approval of regorafenib, these patients had no second-line treatment option. Therefore, this approval provides a treatment option for a patient population with HCC who have an unmet medical need. However, the risk-benefit assessment was considered acceptable primarily because this population has no alternative treatment options, as the treatment effects are modest and regorafenib requires frequent dose modifications for adverse reactions, as discussed below.

The benefits of regorafenib in the RESORCE trial were characterized by a 2.8-month increase in median overall survival, a 1.6-month increase in median PFS, and a 6.5% increase in ORR compared with placebo. These modest benefits were weighed against the toxicities of regorafenib: 10% of patients discontinued regorafenib for adverse reactions, and 48% required dose reductions or interruptions for adverse reactions. Approximately half of the regorafenib-treated patients (51%) experienced PPES; 12% experienced grade 3 PPES, and 41% of patients experienced diarrhea, with grade 3 or 4 diarrhea in less than 5% of patients. Although regorafenib can cause severe hepatotoxicity, regorafenib did not result in an increased incidence of severe (grade 3 or 4) AST, alanine aminotransferase, or hyperbilirubinemia compared with the placebo arm, and no dose adjustment is necessary for patients with Child-Pugh class A liver dysfunction with bilirubin less than or equal to three times the upper limit of normal, based on a population pharmacokinetic analysis of 391 patients with HCC, 275 of whom had mild or moderate hepatic impairment. Patients should be counselled and monitored for serious adverse reactions of hepatotoxicity, infections, hemorrhage, gastrointestinal perforation or fistula, dermatologic toxicity, hypertension, cardiac ischemia or infarction, reversible posterior leukoencephalopathy syndrome, and wound healing complications.

Limitations of this approval are that the safety and efficacy of regorafenib in patients who could not tolerate sorafenib are unknown; however, physicians should be aware that sorafenib and regorafenib have overlapping toxicity profiles. Similarly, there are no data on the safety or efficacy of regorafenib in patients with more advanced cirrhosis (e.g., Child-Pugh class B or C or bilirubin more than three times the upper limit of normal), who were not included in the RESORCE trial.

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This is a U.S. government work. There are no restrictions on its use.

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Disclosures

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